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Date: 18 November 2008

N. T. SIMPKIN
Deputy Managing Director - UK Translation Division
For and on behalf of RWS Group Ltd

[crest]

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File Reference **A 584/2003**

The Austrian Patent Office herewith certifies that

BIOCHEMIE GmbH

of A-6250 Kundl/Tyrol

(Tyrol),

filed a patent application on the **16 April 2003**

relating to

"Organic compounds",

and that the attached description entirely agrees with the original description filed simultaneously with this Patent Application.

Austrian Patent Office
Vienna, 11 March 2004

The President
pp
[Stamp of the Austrian Patent Office]
[signature]

HRNCIR
Senior Technical Inspector

[Seal of the Austrian Patent Office]

A 584/2003 **ORIGINAL TEXT**

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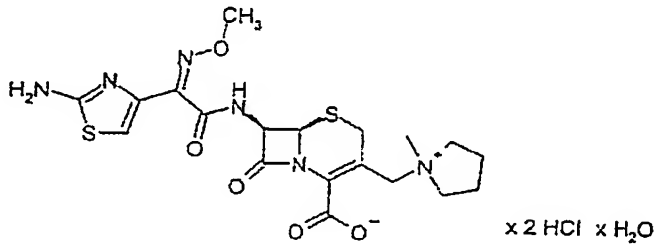
Organic compounds

The present invention relates to the preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride



I

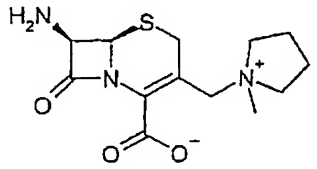
monohydrate). Cefepime is a valuable 4th generation injectable cephalosporin with antibacterial properties, see e.g. The Merck Index Thirteenth Edition, Item 1935.

The preparation of cefepime is not simple. For example, it is known that the 7-acyl side chain as the difficult-to-obtain 2-(2-aminothiazol-4-yl)-2-methoxyimino-acetic acid chloride hydrochloride must be used for the production of cefepime, in order to obtain an active ingredient which is pure in respect of the by-products anti-isomer and Δ-2 isomer.

A novel process for the production of cefepime has been found which is notable for the simplicity of the choice of solvent and the accessibility and easy handling of the 7-acyl side chain, and which at the same time leads to an active ingredient with high purity in respect of the abovementioned by-products.

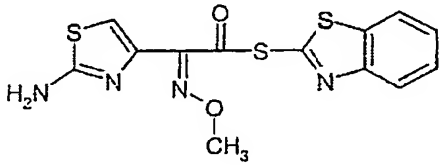
The process comprises the reaction of a pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-

oct-2-en-yl)methyl]-halide, an acid addition salt thereof or its free base of formula II



II

wherein n is 0-2 and X is chloride, bromide or iodide with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-2-mercaptobenzothiazolylester of formula III



III

in an acetonic or aqueous/acetonic solution, optionally in the presence of a base, wherein cefepime dihydrochloride monohydrate is isolated directly from the reaction mixture by adding HCl.

The process is extremely simple.

Neither extraction steps nor more complex purification operations are necessary.

The solvent regeneration is an especially simple procedure, in that only one solvent is used both for the acylation reaction and for the crystallisation step.

The intermediate compound of formula II may be present as mono-addition salt or di-addition salt. In addition, the intermediate of formula II may be present in the form of a solvate, for example a hydrate. The usual addition-salts are represented by the mono- and dihydrochloride or the hydriodide.

Depending on the salt form, the corresponding acid addition salt is released for the reaction with the acylation agent with the assistance of the necessary amount of a base, preferably a trialkylamine. Accordingly, a mono-addition salt is released with approximately one molar equivalent of base, and a di-addition salt is correspondingly released with approximately two. However, it is also possible to react the corresponding acid addition salt with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-2-mercapto-benzothiazolylester without adding a base.

If the intermediate of formula II is used as the mono- or dihydrochloride, the active ingredient cefepime is naturally obtained as the pure dihydrochloride. If the intermediate is used as the hydriodide, the recrystallised product is practically free from traces of iodide.

Alternatively, foreign ions can be removed from the reaction solutions by methods known per se, for example with the assistance of an anion exchanger.

Suitable trialkylamines are C_1-C_8-trialkylamines, for example triethylamine or tributylamine. The presence of water in the acylation reaction in principle also allows the use of inorganic bases, for example sodium or potassium hydroxide or an alkali hydrogen carbonate or alkali carbonate.

The reaction is preferably carried out in the presence of water: the amount of water is not critical; there must be balanced solubility of the cephalosporin intermediate of formula II on the one hand and of the active ester of formula III on the other hand. The water/acetone ratio is about 1:10 to 10:1, and preferably a water/acetone ratio of 1:1 to 1:5 is used for the acylation reaction. After the acylation reaction, in order to crystallise cefepime dihydrochloride, hydrochloric acid is added, preferably aqueous concentrated hydrochloric acid, and a pH value of less than 3, preferably less than 1, is set. By adding acetone, the crystallisation of cefepime dihydrochloride is then completed. Preferred water/acetone ratios in the crystallisation step are ratios of 1:1 to 1:20, especially ratios of 1:3 to 1:10.

The examples below elucidate the invention in more detail.

Example 1

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-pyrrolidinium dihydrochloride hydrate

44.3 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate (NMP-ACA) are suspended in a mixture of 200 ml of H_2O and 400 ml of acetone. 38.5 g of (Z)-(2-aminothiazol-4-yl)methoxy-iminoacetic acid-2-mercapto-benzothiazolylester are added to the suspension. At a temperature of ca. 15°C, a mixture of 13.9 ml of triethylamine and 14 ml of acetone is slowly added dropwise to the suspension over the course of 3 hours.

The resulting cloudy solution is stirred for a total of 6.5 hours at 20°C.

33 ml of 37% HCl are subsequently added to the reaction mixture, and then ca. 300 ml of acetone are added whilst stirring. The mixture is seeded with seed crystals, and within ca. 90 minutes a suspension is produced. Subsequently, within 90 minutes, 1700 ml of acetone are added dropwise whilst stirring gently. The suspension is stirred for a further one hour at room temperature, and then the title compound is isolated through a suction filter, and the product is washed with 250 ml of acetone/H_2O mixture (90/10) and with a total of 500 ml of acetone in two portions. The product is subsequently dried for ca. 18 hours at room temperature in a vacuum drying chamber.

Yield 51.8 g
purity: HPLC: 98.8 area percent

Example 2

Recrystallisation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium dihydrochloride hydrate

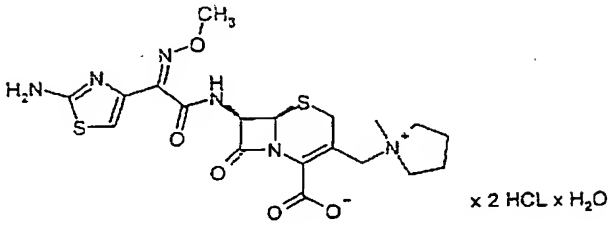
50.0 g of cefepime dihydrochloride hydrate are dissolved in 200 ml of H_2O. 22 ml of 6 n HCl are added and then the solution is mixed with 5 g of activated carbon. The suspension is stirred for 10 minutes at room temperature and then filtered through a suction filter. The filter layer is then washed with 50 ml of H_2O, and the combined filtrates are mixed with 600 ml of acetone until turbidity occurs. The resulting suspension is stirred for 15 minutes and then a further 1400 ml of acetone are added over the course of one hour whilst stirring gently. The suspension is stirred for another one hour at room temperature, and the

product is subsequently isolated through a suction filter. The product is washed with a total of 500 ml of acetone and dried for ca. 18 hours at room temperature in a vacuum drying chamber.

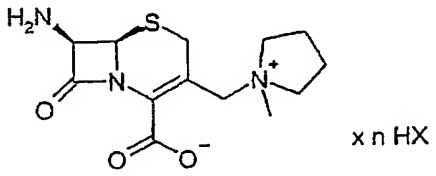
Yield	45.01 g
purity HPLC:	99.7 area percent

Claims

1. A process for producing the compound of formula I

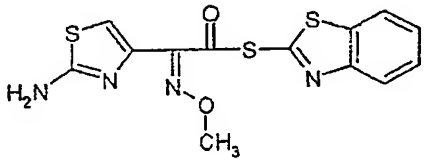


wherein a compound of formula II



wherein X is chloride or iodide and n is 0 to 2 in unsolvated or solvated form is reacted optionally after addition of a base with the compound of formula III

III



in acetone or aqueous acetone and the compound of formula I is isolated from the reaction mixture by addition of HCl.

2. A process as claimed in claim 1, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-

azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate is used.

3. A process as claimed in claim 1, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-yl)methyl]-chloride is used, optionally in solvated form.

4. A process as claimed in claim 1, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride is used, optionally in solvated form.

5. A process as claimed in any one of claims 1 to 4, wherein a C_1-C_8-trialkylamine, KOH or NaOH, or an alkali hydrogen carbonate or potassium carbonate, is used as the base.

Biochemie GmbH
[signature]